

Original article

Effectivity of combined diffusion-weighted imaging and contrast-enhanced MRI in malignant and benign breast lesions

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Abstract

Purpose: Mammography is the most commonly used diagnostic test for breast lesion detection and evaluation, but in dense breast parenchyma it lowers its sensitivity to detect small lesions. Sensitivity and specificity improves with combined use of contrast-enhanced magnetic resonance imaging (CE-MRI) and diffusion-weighted imaging (DWI) in differentiating benign and malignant breast lesions. The aim of the study was to evaluate the effectivity of combined dynamic CE-MRI and DWI in differentiating benign and malignant lesions, and to calculate the apparent diffusion coefficient (ADC) values of malignant and benign lesions of the breast.

Material and methods: Fifty-seven patients with 68 lesions were included in the study. MRI of breast using different sequences was acquired on 1.5 Tesla Machine with dedicated breast coils. Dynamic CE-MRI along with DWI was acquired for each patient. Histopathological reports were accepted as the standard of reference.

Results: Out of 68 lesions, 37 were malignant on biopsy (54.4%) and 31 were benign (45.5%). The sensitivity of CE-MRI was 92%, specificity 84.21%, positive predictive values (PPV) 88.46 %, and negative predictive values (NPP) 88.89%. The sensitivity of DWI-MRI was 91.6%, specificity was 90.6%, PPV 91.6%, and NPP 90.6%. The sensitivity of combined DWI-MRI and CE-MRI was 95.0%, specificity was 96.43%, PPV 97.44%, and NPP 93.10%. Mean ADCs of benign lesions ($b = 800$) was $1.905 \pm 0.59 \times 10^{-3} \text{ mm}^2/\text{s}$, which was significantly higher than those of malignant lesions ($b = 800$) $1.014 \pm 0.47 \times 10^{-3} \text{ mm}^2/\text{s}$.

Conclusion: Multi-parametric MRI is an excellent non-invasive modality with high sensitivity and specificity to differentiate malignant from benign breast lesions.

Key words: carcinoma, breast, fibroadenoma, magnetic resonance imaging.

Introduction

Breast cancer is the most common cancer diagnosed and is the second leading cause of death [1]. According to Surveillance Epidemiology and End Results Program (SEER), there were 246,660 estimated new cases of breast cancer in 2016, which accounts for 14.6% of all new cancer cases. Breast cancer resulted in 40,450 estimated deaths in 2016, which constituted 6.8% of all cancer deaths [2]. Cancer of the breast, with an estimated 150,000 (over 10% of all

cancers) new cases during 2016, is the number one cancer overall [3]. The high prevalence and need for early treatment of breast malignancy emphasises the need for early and accurate diagnosis.

Contrast-enhanced magnetic resonance imaging (CE-MRI) of the breast is currently the most sensitive detection technique for diagnosis of breast cancer. Various comparative studies have demonstrated that breast MRI has the same specificity as mammography and higher specificity than breast ultrasound, while many other stud-

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A Study design · B Data collection · C Statistical analysis · D Data interpretation · E Manuscript preparation · F Literature search · G Funds collection

ies have suggested a lower specificity and positive predictive value.

Dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted imaging (DWI) are excellent non-invasive techniques that are very useful in differentiating malignant from benign pathologies of the breast. Morphological analysis and enhancement pattern with kinetic curves are helpful in the characterisation of the lesion.

Morphological analysis of breast lesions was done according to BIRADS MRI lexicon by evaluation of the shape, margin, and enhancement characteristics [4].

DWI is an MRI technique that employs the differential diffusion rate of water molecules in normal and pathologic tissue. This technique has a higher specificity to differentiate between benign and malignant breast lesions compared to that of CE-MRI (84% compared to 37%) [5]. The differences in cellularity are used to distinguish malignant from benign lesions because malignant lesions, which have a higher degree of cellularity, show restricted diffusion.

We present a prospective analysis of 57 patients with 68 breast lesions, who underwent breast MRI for evaluation of breast cancer. This study emphasises the role of DCE-MRI, enhancement curves, DWI, and the apparent diffusion coefficient (ADC) value in differentiating benign and malignant lesions of the breast.

Material and methods

This is a prospective study carried out between November 2014 and November 2016 in the Department of Radiology and Imaging in the University Hospital. A total of 68 female patients were included in the study, with an age range of 20-68 years and mean age of 42.6 years. All records including the clinical presentation, MRI findings, kinetic curves, and ADC values were correlated with cytological or histopathological reports.

Inclusion criteria: Patients with breast mass lesions and architectural distortion detected on mammography or on ultrasonography of the breast. Micro-calcification and/or architectural distortion detected on mammography. Patients with clinically palpable lump.

Exclusion criteria: Patients without detectable lesion on MRI breast, patients without histological confirmation of breast lesion, known allergy to gadolinium-based contrast media, patients who are currently pregnant, with abnormal kidney functions tests, and patients having prosthetic heart valves, cardiac pacemakers, cochlear implants, or any metallic implants.

Imaging was done on a Siemens Avanto Magnetic Resonance Imaging 1.5 Tesla Machine using dedicated double breast coils. No compression was applied. For routine MRI examinations of the breast, the patient was put in a prone position. MRI examination included image acquisition followed by post processing. Field of view (FOV) was 300-360 mm and slice thickness was 3 mm.

The following sequences were obtained: T1WI, T2WI, and STIR in the axial plane, STIR, T2WI coronal, T2WI, and STIR in the sagittal plane. DWI were obtained using echo-planar imaging, and sensitising diffusion gradients with b value of 0.400 and 800 s/mm² were applied. Dynamic study of post gadolinium T1WI fat saturation was obtained in the axial plane. Pre-contrast fat-suppressed T1W gradient echo images were obtained, and this was followed by intravenous contrast injection. MultiHance (GdDTPA-BMA) 0.1 mmol/kg body weight was injected as a bolus with a flow rate of 2.0 ml/s, followed by a flush of 20 ml saline. Gradient-echo images were obtained at one minute and two minutes, and again at six minutes and seven minutes. Post processing was done by digitally subtracting the pre-contrast images from the sequential post contrast images. Maximum intensity projection (MIP) was obtained through each orthogonal plane. Kinetic analysis was done using the mean curve technique. MRI interpretation was done by analysing the pre-contrast and post-contrast images and post processing data. Initially, STIR images were analysed to detect the presence of lesions or cysts. The type of post-contrast enhancement was observed (mass or non-mass like enhancement). Types of kinetic curves were defined according to three types of enhancement curves. Type I is the persistent delayed type of enhancement, which continued with an increased signal intensity throughout the dynamic phase. Type II reached a plateau during which signal intensity did not change in the delayed phase. Type III curve had early wash out in the delayed phase. All the patients were followed-up for histopathology correlation.

Results

The study was carried out in 57 patients with 68 breast lesions. Statistical calculation was done by software OpenEpi, Version 3. The mean age of all the patients who were part of the study was 42.6 ± 13.2 years with the age range of 20-68 years. Histopathology analysis of 68 breast lesions revealed malignant lesions in 37 lesions, constituting 54.4% of total lesions, and 31 lesions were benign, constituting 45.5% of total lesions. The mean age of the women who constituted the benign lesions was 36.9 ± 5.2 years, whereas the mean age of women with malignant lesions was 47.4 ± 4.6 years. The upper outer quadrant was the most common region affected by malignancy.

The histological types of 31 benign lesions were 14 fibroadenoma (45.16%) (Figure 1), seven were cysts (22.58%) (Figure 2), five were mastitis (16.12%) (Figure 3), two were fat necrosis (6.45%), and three lesions were phyllodes (9.6%).

In 37 cases of malignant lesions invasive ductal carcinoma was the most common pathology in 17 lesions (45.94%) (Figure 4) followed by invasive lobular carcinoma in 11 lesions (29.72%) (Figure 5), ductal carcinoma in situ in six (16.21%) (Figure 6), mucinous carcinoma

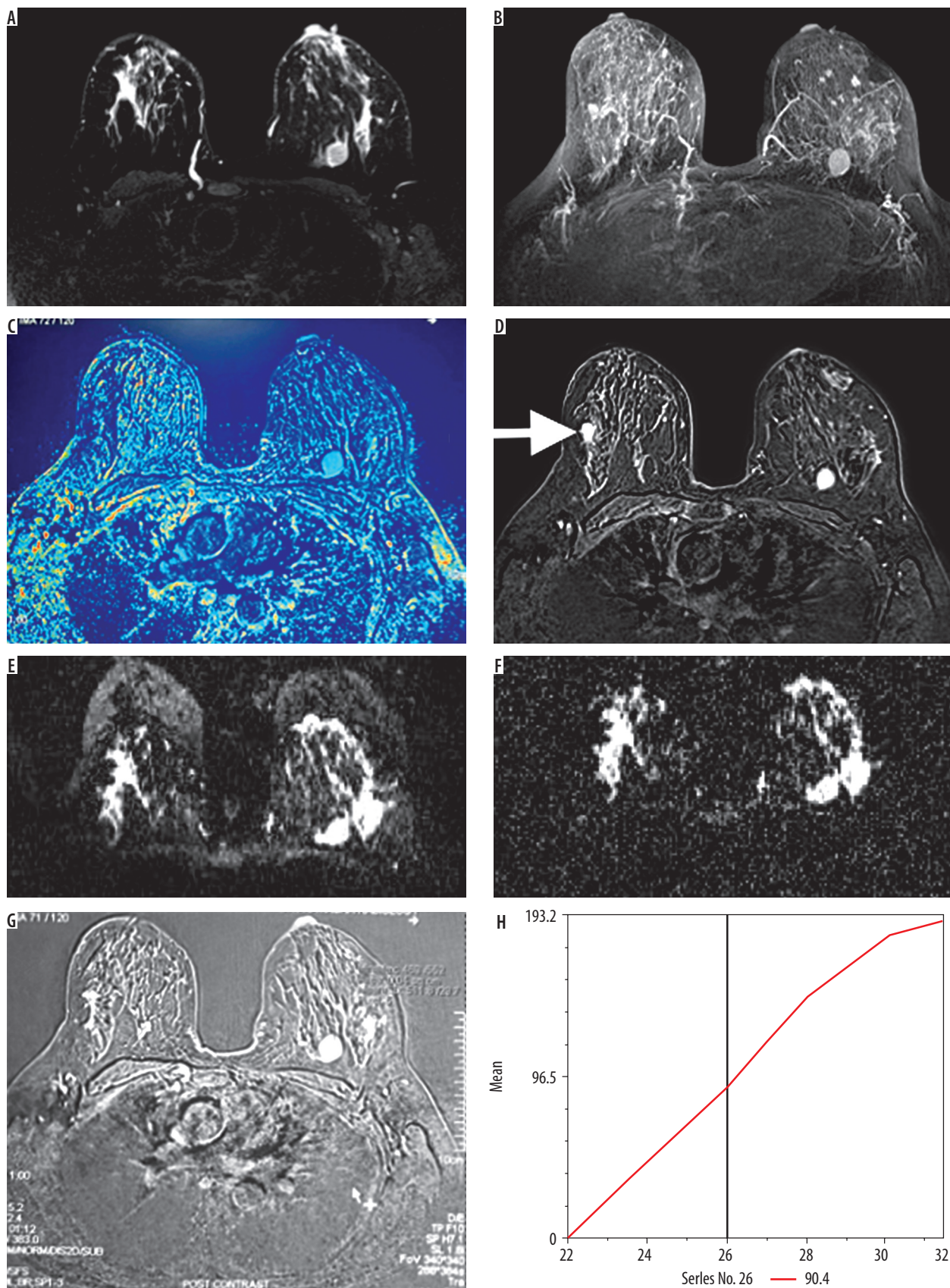


Figure 1. Magnetic resonance imaging breast in the case of fibroadenoma in a 39-year-old woman. **A)** Axial STIR image of breast showing a well-defined oval hyperintense lesion with smooth margins in the retromammary region of the left breast. **B)** Maximum intensity projection image showing the smooth margin oval lesion. **C)** Wash-in colour map maximum intensity projection image showing the smooth margin oval lesion. **D)** Fat sat T1WI post contrast axial image showing homogenous contrast enhancement of the lesion in the left breast. There is another well-defined fibroadenoma seen in the right breast (arrow). **E)** Axial diffusion weighted imaging showing hyperintense signals in the mass with **F)** corresponding high apparent diffusion coefficient value. **G-H)** Time signal intensity curve of the mass showed type I kinetic curve (persistent enhancement in the delayed phase)

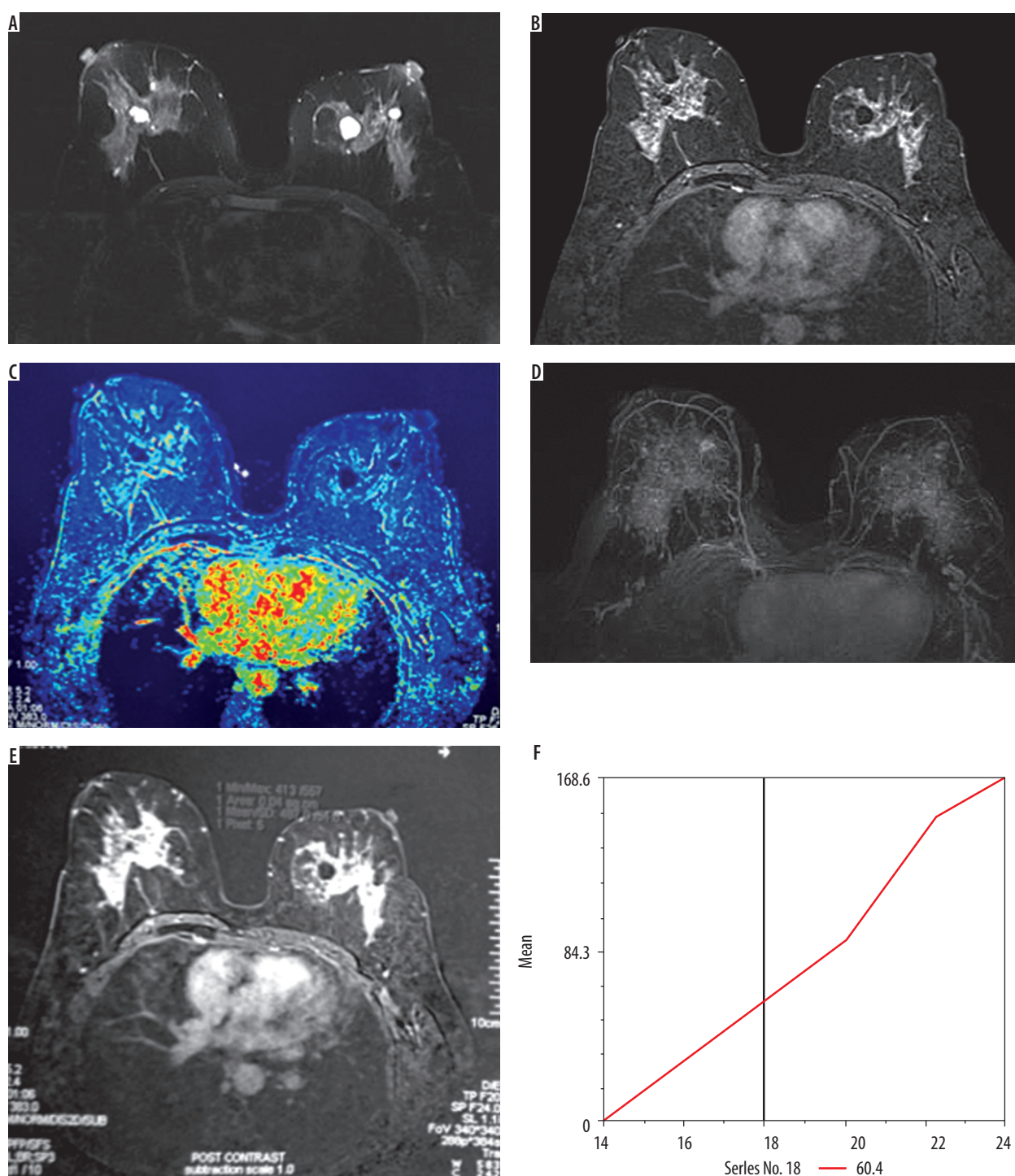


Figure 2. Magnetic resonance imaging breast in a case of multiple cysts in a 45-year-old woman. A) Axial STIR image showing two well defined hyperintense cystic lesions in the left breast and one cystic lesion in the right breast. B) Axial post contrast fat sat T1WI showing no contrast enhancement in the cystic lesions. C) Wash-in colour map and maximum intensity projection image showing the smooth margin oval cystic lesions and no post-contrast enhancement. D) Maximum intensity projection image showing no post contrast enhancement. E-F) Time signal intensity curve of the cystic lesions showed type I kinetic curve (persistent enhancement in the delayed phase)

in two (5.4%), and malignant phyllodes detected in one lesion (2.7%) (Figure 7).

Most of the round or oval lesions (89%) were benign, and 78% of the lobulated lesions were malignant, although 22% of the benign lesions also showed a lobulated outline. All the lesions with speculated margins were malignant on histopathology.

According to the contrast enhancement pattern, three types of basic curve shapes were demonstrated. Type I curves are slowly enhancing with gradual, steady enhancement occurring for about 5 min. Approximately 6% of lesions in our study with a type I curve showed malignancy. Type II curves represent early strong enhancement (increase over a 1-2-min period) with a subsequent pla-

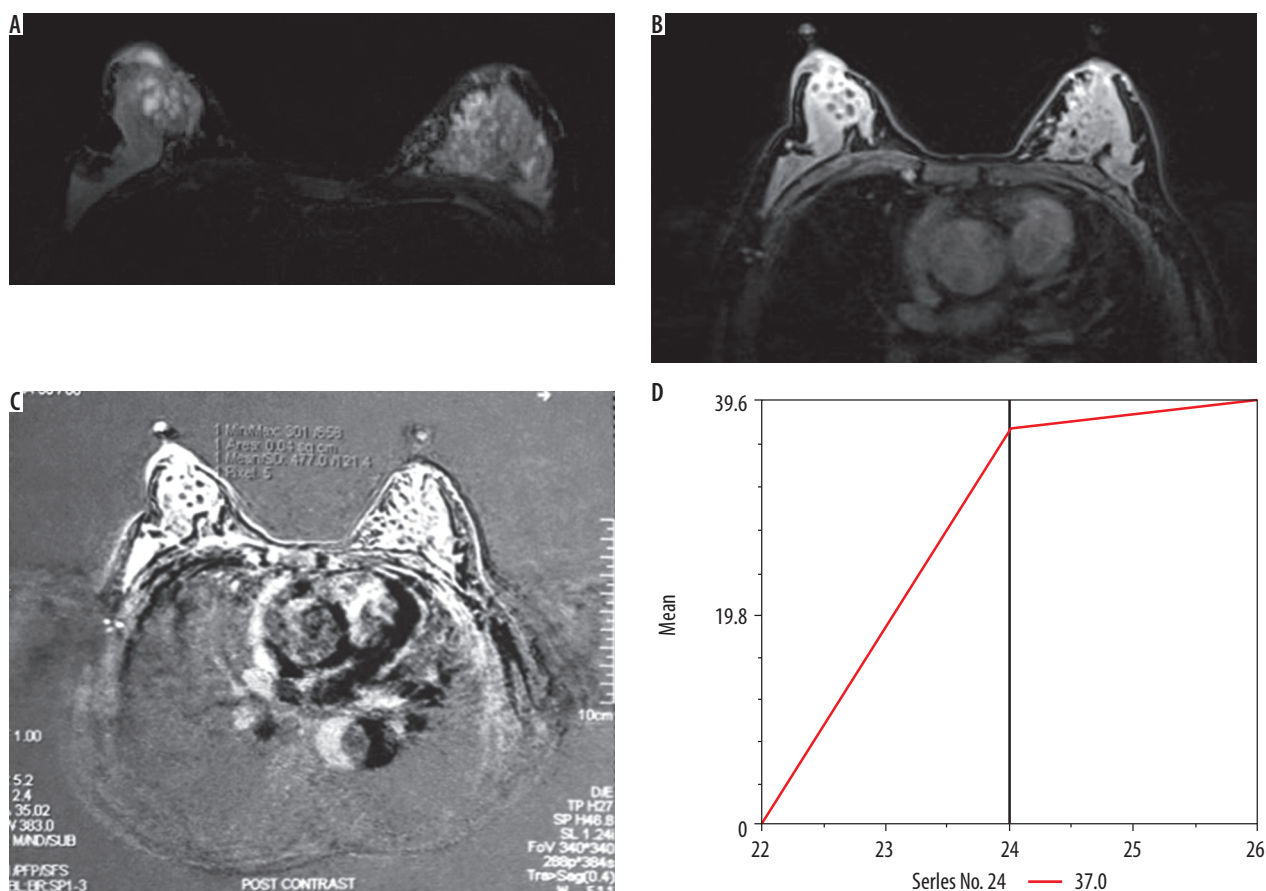


Figure 3. Magnetic resonance imaging breast in a case of mastitis in 38-year-old woman. **A)** Axial STIR image showing an ill-defined heterogeneously hyperintense signal intensity lesion seen in the right breast. **B)** Axial post contrast fat sat T1WI showing heterogenous enhancement of the lesion more on peripheral aspect. **C-D)** Time signal intensity curve of the mass showed type II kinetic curve (plateau)

teau phase. Malignancy was detected in approximately six (29%) lesions with a type II curve. Type III or “washout” curves represent early strong enhancement, with subsequent decline in enhancement, producing a characteristic peak dubbed the “the cancer corner,” and are strongly associated with malignancy. Twenty-nine (77%) breast lesions that were malignant in our study showed type III curve.

Of 68 lesions, 26 showed type III curve (38%), 24 showed type II curve (35%), and 18 lesions demonstrated type I curve (27%) (Figure 8). When considering the types of dynamic contrast-enhancement curves, (time/signal intensity curve), type III curve was noted in 23 malignant lesions. Type II curve was noted in 12 malignant lesions and 12 benign lesions, while type I curve was noted in 16 benign lesions (Table 1). Of all the malignant lesions, 23 cases (62.16%) demonstrated type III curve, type II curve was showed by 12 cases (32.43%), whereas only 2 (5.40%) cases demonstrated type I curve. In benign cases type I curve was seen in 16 cases (51.61%), type II curve was seen in 12 (38.70%) cases, and type III was seen in three cases (9.67%) (Table 2). The sensitivity of type III curve alone to detect malignant lesions was 92% (95% CI: 75.03-97.78), specificity 84.21% (95% CI: 62.43-94.48),

positive predictive values (PPV) 88.46 %, negative predictive values (NPP) 88.89% (Figure 9).

According to the side, there were 30 lesions on the left breast, of which 16 were malignant and 14 were benign. There were 34 lesions seen on the right breast, of which 19 were malignant and 16 were benign. In four cases there were lesions seen in bilateral breast; one was malignant and three were benign.

According to the site, the upper outer quadrant was the most common site for malignant and benign lesions, seen in 21 malignant lesions (56%) and in 16 benign cases (51%).

DWI was done in all 68 cases, and lesions showing diffusion restriction were considered positive, whereas lesions not showing restriction were considered negative. Thirty-three (89%) of the malignant lesions showed diffusion restriction, with corresponding low ADC values, and 29 (87%) of the benign lesions did not show restriction on diffusion, with corresponding high ADC values (Table 3). We localised the lesion and calculated the ADC values in all the lesions. The sensitivity of DWI-MRI was 91.6% (95% CI: 78.17-97.13), specificity was 90.63% (95% CI: 75.78-96.76), PPV 91.6%, NPP 90.6% (Figure 10, Table 3). Mean ADCs of benign lesions ($b = 800$) was 1.905 ± 0.59

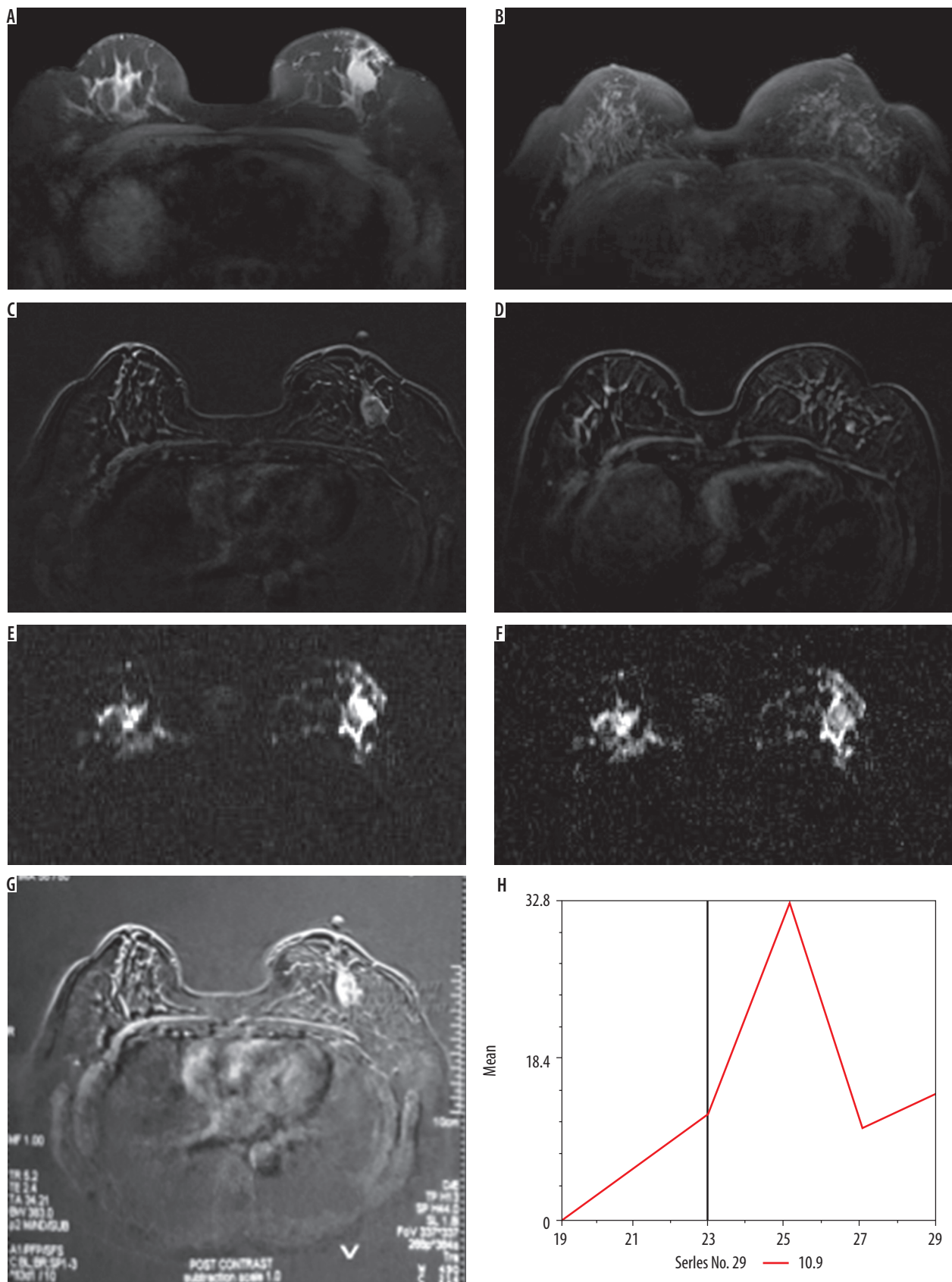


Figure 4. Magnetic resonance breast imaging in a case of invasive ductal carcinoma in a 46-year-old woman. **A)** Fat sat axial T1WI showing a well-defined oval, irregular mass lesion with speculated margins seen in the left breast. **B)** Maximum intensity projection image showing rim enhancement of the lesion. **C)** Fat sat axial T1W post contrast image showing rim enhancement of the mass lesion. **D)** Fat sat axial T1W post contrast image showing a small enhancing non-mass area adjacent to the mass, which was not detected on mammogram, tomosynthesis, or in ultrasound of the breast. **E)** Axial diffusion-weighted imaging showing hyperintense signals in the mass with **F)** corresponding low apparent diffusion coefficient value (restriction on diffusion weighted imaging). **G-H)** Time signal intensity curve of the mass showed type III kinetic curve (early washout)

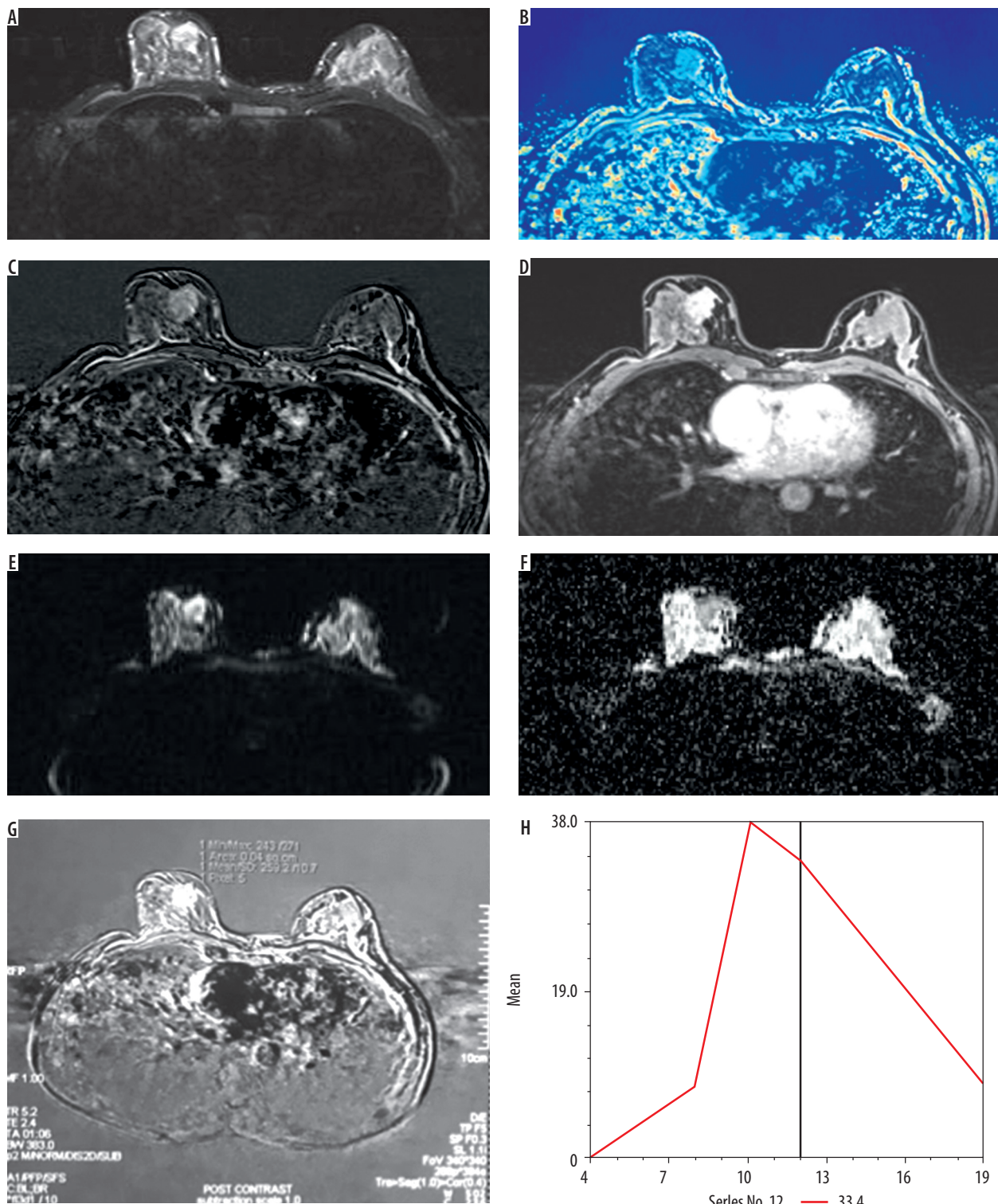


Figure 5. Magnetic resonance breast imaging in a case of invasive lobular carcinoma in a 52-year-old woman. A) Axial STIR image of the breast showing a well-defined irregular mildly hyperintense mass seen in the right breast with lobulated margins. B) Wash-in colour showing early enhancement of the mass (C) and post contrast (D). Axial fat sat T1WI image showing early enhancement of the mass. E) Axial diffusion weighted imaging (DWI) showing hyperintense signals in the mass with f: corresponding low apparent diffusion coefficient value (restriction on DWI). G-H) Time signal intensity curve of the mass showed type III kinetic curve (early washout)

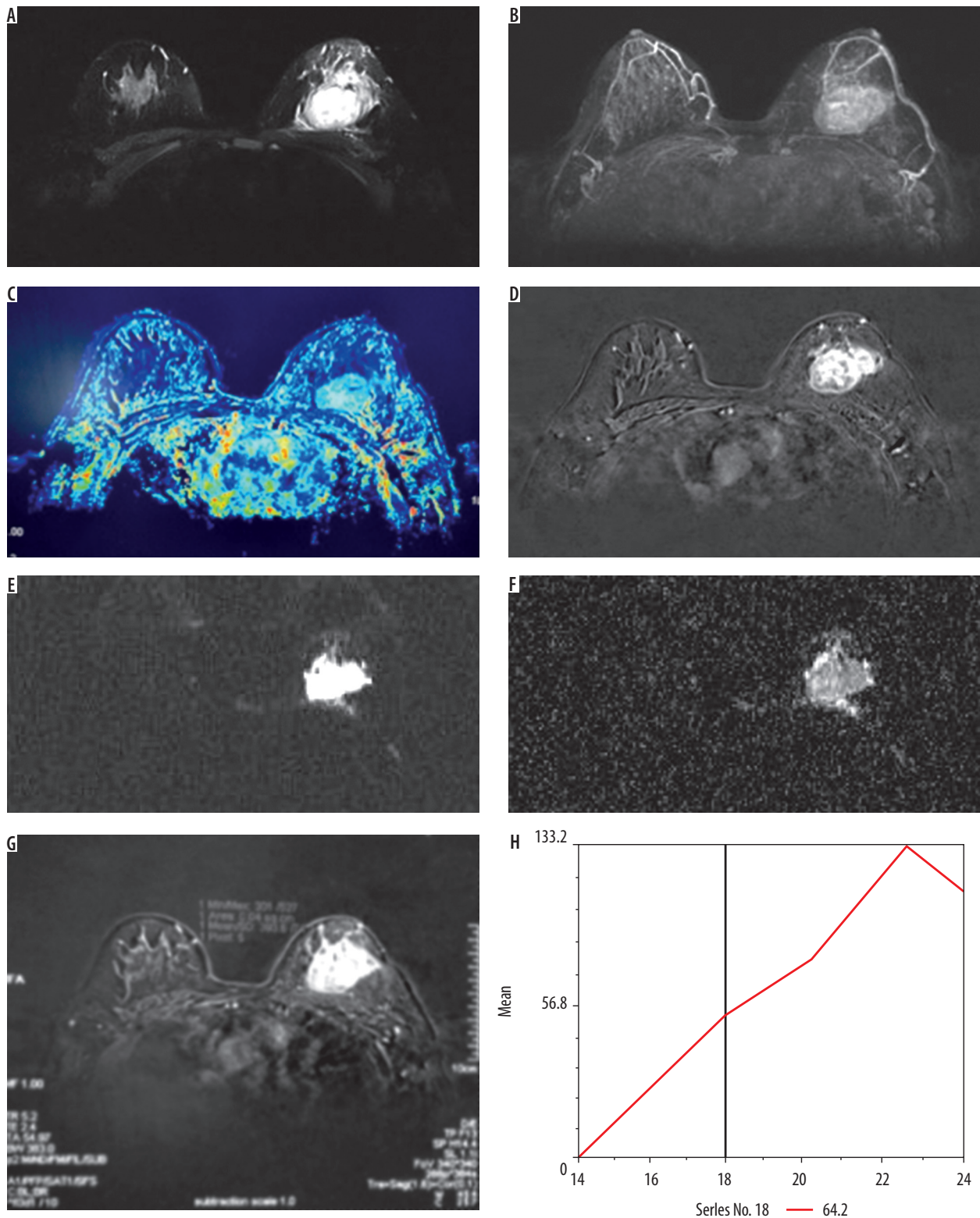


Figure 6. Magnetic resonance breast imaging in a case of ductal carcinoma in situ in a 65-year-old woman. A) Axial STIR image of the breast showing a well-defined heterogeneous, hyperintense mass seen in the left breast. B) Maximum intensity projection image showing heterogeneous enhancement of the lesion. C) Wash-in colour map. D) Post-contrast axial fat sat T1WI image showing intense heterogeneous enhancement of the mass. E) Axial diffusion weighted imaging (DWI) showing hyperintense signals in the mass with F) corresponding low apparent diffusion coefficient value (restriction on DWI). G-H) Time signal intensity curve of the mass showed type III kinetic curve (early washout)

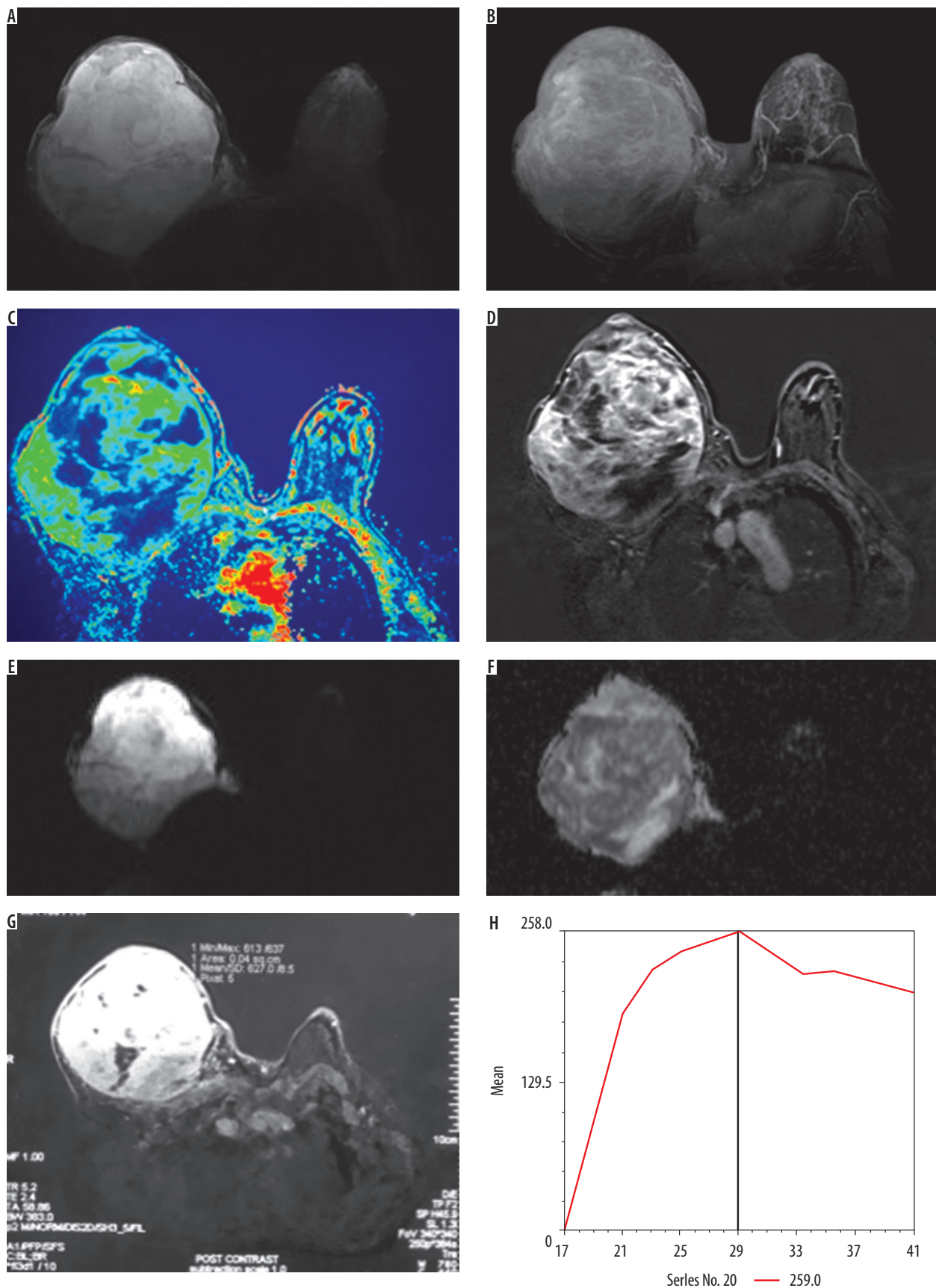


Figure 7. Magnetic resonance imaging breast in a case of malignant phyllodes in a 40-year-old woman. A) Axial T2WI showing a large heterogeneous mass in the right breast. B) Maximum intensity projection image showing heterogeneous enhancement of the lesion. C) Wash-in colour map showing early enhancement of the mass. D) Post-contrast axial fat sat T1WI image showing intense heterogeneous enhancement of the mass. E) Axial diffusion weighted imaging (DWI) showing hyperintense signals in the mass with F) corresponding low apparent diffusion coefficient value (restriction on DWI). G-H) Time signal intensity curve of the mass showed type III kinetic curve (early washout)

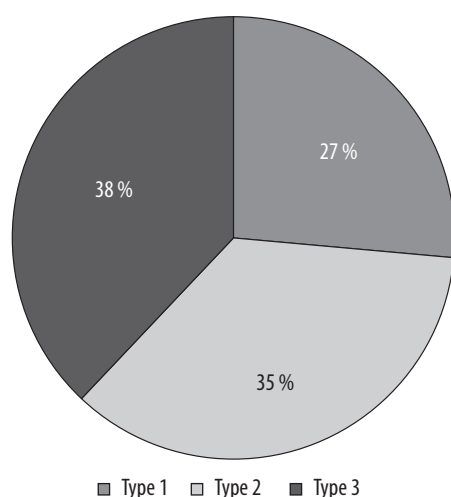


Figure 8. Pie chart of the breast lesions demonstrating types of kinetic curves. Out of 68 lesions, 26 showed type III curve (38%), 24 lesions showed type II curve (35%), and 18 lesions demonstrated type I curve (27%)

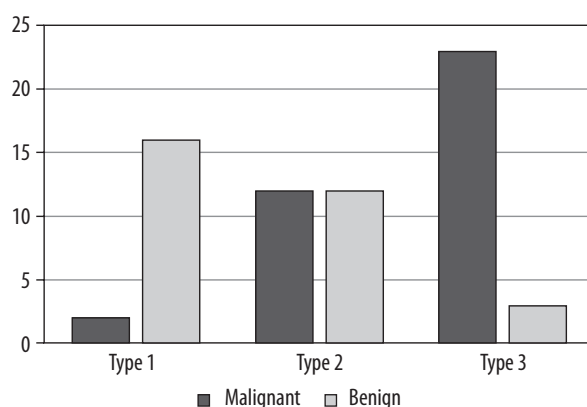


Figure 9. Bar chart of types of kinetic curves seen in malignant and benign lesions of the breast. The sensitivity of type III curve alone to detect malignant lesions was 88.46%. The sensitivity of contrast-enhanced magnetic resonance imaging was 86.1%, specificity was 93.75%, positive predictive value 93.9%, negative predictive value 85.7%

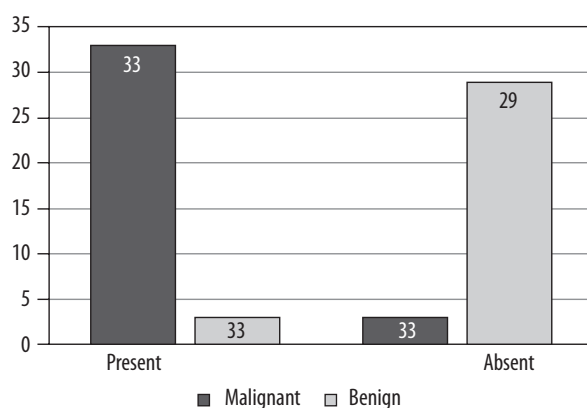


Figure 10. Bar chart showing the diffusion weighted imaging result in malignant and benign breast lesions. The sensitivity of diffusion-weighted magnetic resonance imaging was 91.6%, specificity was 90.6%, positive predictive value 91.6%, negative predictive value 90.6%

Table 1. Kinetic curves/biopsy result: number of lesions showing type II and type III kinetic curve and type I kinetic curve in malignant and benign lesions

| Kinetic curve/Biopsy | Positive | Negative | Total |
|----------------------|----------|----------|-------|
| Type II, III | 35 | 15 | 50 |
| Type I | 2 | 16 | 18 |
| Total | 37 | 31 | 68 |

Table 2. Types of kinetic curves seen in 37 malignant and 31 benign lesions

| Type | Groups | | | | Total | |
|-------|-----------|-------|--------|-------|-------|-------|
| | Malignant | | Benign | | No. | % |
| | No. | % | No. | % | No. | % |
| I | 2 | 5.40 | 16 | 51.61 | 18 | 26.47 |
| II | 12 | 32.43 | 12 | 38.70 | 24 | 35.29 |
| III | 23 | 62.16 | 3 | 9.67 | 26 | 38.23 |
| Total | 37 | — | 31 | — | 68 | |

Table 3. Number of DWI restriction cases and biopsy result in 37 malignant and 31 benign lesions

| DWI restriction/Biopsy | Positive | Negative | Total |
|------------------------|----------|----------|-------|
| Present | 33 | 3 | 36 |
| Absent | 3 | 29 | 32 |
| Total | 36 | 32 | 68 |

$\times 10^{-3}$ mm (2)/s, which was significantly higher than those of malignant lesions ($b = 800$) was $1.014 \pm 0.47 \times 10^{-3}$ mm (2)/s.

The sensitivity of combined DWI-MRI and CE-MRI was 95.0% (95% CI: 83.5-98.62) and specificity was 96.43% (95% CI: 82.29-99.37), PPV 97.44%, NPP 93.10%.

Discussion

In a study done in 2002, Tillman *et al.* determined the impact of breast MRI on the clinical management of patients with early stage breast cancer. The study found that in 20% of their 212 diagnosed breast cancers clinical management was changed based on the MRI findings. There was a strongly favourable effect on management in 8%, a somewhat favourable effect in 3%, a somewhat unfavourable effect in 5%, and a strongly unfavourable effect in 1%. The study concluded that breast MRI appears to offer clinically useful information for determining optimal local treatment [6]. It is comparable to our study, which also showed a favourable effect on better evaluation of the breast lesions.

In our study the most common malignant pathology was invasive ductal carcinoma in 17 lesions (45.94%), followed by invasive lobular carcinoma in 11 lesions (29.72%). The two most common benign lesions were

fibroadenoma (45.16%) and cysts (22.58%). It matches with the results obtained by Li *et al.*, who showed in their breast lesion survey that invasive ductal carcinoma accounts for 56%, fibroadenoma 20%, and invasive lobular carcinoma only 10% [7].

In our study the most common location for breast lesions was the upper outer quadrant, in 56% of malignant and 51% of benign lesions. It matches the study done by Mahoney and Darbre, who stated that the most common location for malignant and benign lesions is in the upper outer quadrant, which may be due to the large amount of glandular tissue present in this region [8,9].

In our study most of the benign lesions showed oval or round shape, while most malignant lesions were irregular in shape. It is comparable to Wedegartner *et al.* and Tozaki *et al.*, who showed that most benign lesions have ovoid or rounded shape while malignant lesions have irregular shape [10, 11].

In our study type III wash-out curve was seen in 62% of malignant cases. Type II plateau curve was seen in 32% of malignant cases, and type I persistent curve in 5.4% of malignant cases. Type I curve was seen in 51% of benign lesions, type II curve was seen in 38% of benign cases, and type III curve was seen in 9.6% of benign cases. These results matched those of Kul *et al.*, who showed that type I persistent curve was seen in 81.1% of benign lesions and 12.8% of malignant lesions, type II plateau curve was seen in 10.8% of benign lesions and 40.4% of malignant lesions, and type III wash-out curve was seen in 8.1% of benign lesions and 44.7% of malignant lesions [4].

In a study done by Chakraborti *et al.* in 2005, 50 patients with suspected breast mass lesion (40 palpable and 10 non-palpable) were selected for the study. Both mammography and MRI (plain and contrast-enhanced) were performed in every patient. The result of the study showed that for non-palpable lesions the sensitivity of mammography and MRI was 65% and 90%, while the specificity was 25% and 50%, respectively. For palpable lesions both methods showed high sensitivity (mammography 90% and MRI 95%), and MRI demonstrated comparatively higher specificity (mammography 30% and MRI 50%). With complementary use of MRI, it is possible to increase the sensitivity for detection of breast cancer and multicentric disease. In patients in whom the status of a palpable breast mass remains unclear but where strong clinical suspicion exists, MRI may help to reduce the number of unnecessary biopsies [12]. Our study also had a higher sensitivity of MRI. The sensitivity of CE-MRI was 86.1% and specificity was 93.75%.

Another study done in 2007 by Mijung Park and Eun Suk Cha on 41 patients showed that DWI has a high sensitivity for detecting breast tumours and specificity for detecting malignant breast tumours. DWI was an effective imaging technique for detecting breast lesions, as compared using the T1- and T2-weighted images [13].

In 2011 a study was done by Kul *et al.* to evaluate the role of an imaging protocol that combines DCE-MRI and DWI in patients with suspicious breast lesions [4]. In this study, 84 patients with breast tumours (37 benign, 47 malignant) underwent DCE-MRI and DWI before biopsy. Diagnostic values of DCE-MRI, DWI, and combined MRI were calculated [4]. ADC gave 91.5% sensitivity and 86.5% specificity. DCE-MRI alone showed 97.9% sensitivity and 75.7% specificity. The combination of DCE-MRI with DWI gave 95.7% sensitivity and 89.2% specificity [4]. In our study, DCE-MRI alone showed 86.1% sensitivity and 93.75% specificity. In our study, the sensitivity of combined DWI-MRI and CE-MRI was 95.0% and the specificity was 96.43%. This suggests that by combining the two methods, the detection of false positive cases decreases significantly [4].

Another study done by Bakry *et al.* in 2015, to evaluate the role of DWI and DCE-MRI in characterisation of breast tumours, showed a sensitivity of 91.7% and a specificity of 84.2% for DCE-MRI alone [14]. The diffusion-weighted MRI showed a sensitivity of 94.4% and a specificity of 92.1%. The combined use of DCE-MRI and DWI increased the sensitivity and specificity of breast MRI for the detection of breast tumours. The sensitivity and specificity of DWI-MRI was slightly higher than the given study (sensitivity of 92.8% and specificity of 91.6%). However, the sensitivity of DCE-MRI was low compared to the given study. The sensitivity of CE-MRI was 78.5% and specificity was 75%.

Our study disagrees with a study done by Gianfelice *et al.*, who reported that the sensitivity and specificity of DCE-MRI were 90% and 67%, respectively.

In a study done in 2014 by Hetta, to assess the impact of diffusion-weighted images as a complementary tool to conventional breast MRI in the evaluation of various breast lesions, DCE-MRI showed a sensitivity of 80% and a specificity of 73.33% [5], which was comparable to our study. In the same study, the benign lesions showed a mean ADC value of 1.38 ± 0.26 , whereas the malignant lesions showed a mean ADC value of 1.03 ± 0.35 . In comparison, the mean ADC value of benign lesions was 1.135 ± 0.59 , which was significantly higher than those of malignant lesions 0.611 ± 0.47 [7]. In our study, mean ADC of benign lesions was $1.905 \pm 0.59 \times 10^{-3} \text{ mm}^2/\text{s}$, which was significantly higher than those of malignant lesions, at $1.014 \pm 0.47 \times 10^{-3} \text{ mm}^2/\text{s}$.

In our study we added the combined use of DWI and CE-MRI, which increased the sensitivity and specificity of the breast MRI. We evaluated the ADC values of the benign and malignant lesions, which was helpful to differentiate the benign and malignant pathologies.

Conflict of interest

The authors report no conflict of interest.

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